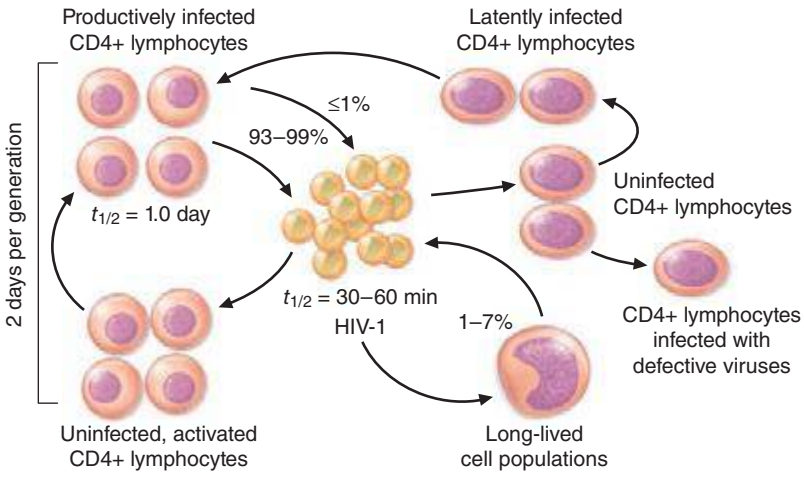

FIGURE 226-21 Dynamics of HIV infection in vivo. See text for detailed description. *(From AS Perelson et al: Science 271:1582, 1996.)*

killing of CD4+ T cells was linked directly to the levels of replicating virus. However, a significant component of the early rise in CD4+ T cell numbers following the initiation of therapy may be due to the redistribution of cells into the peripheral blood from other tissue compartments throughout the body as a consequence of therapy-related diminution in viremia-associated immune system activation. It was determined on the basis of modeling the kinetics of viral decline and the emergence of resistant mutants during therapy that 93–99% of the circulating virus originated from recently infected, rapidly turning over CD4+ T cells and that ~1–7% of circulating virus originated from longer-lived cells, likely monocytes/macrophages. A negligible amount of circulating virus originated from the pool of latently infected cells (Fig. 226-21). It was also determined that the half-life of a circulating virion was ~30–60 min and that of productively infected cells was 1 day. Given the relatively steady level of plasma viremia and of infected cells, it appears that extremely large amounts of virus (~10^{10}–10^{11} virions) are produced and cleared from the circulation each day. In addition, data suggest that the minimal duration of the HIV-1 replication cycle in vivo is ~2 days. Other studies have demonstrated that the decrease in plasma viremia that results from cART correlates closely with a decrease in virus replication in lymph nodes, further confirming that lymphoid tissue is the main site of HIV replication and the main source of plasma viremia.

The level of steady-state viremia, called the viral *set point*, at ~1 year following acquisition of HIV infection has important prognostic implications for the progression of HIV disease in the untreated patient. It has been demonstrated that as a group untreated HIV-infected individuals who have a low set point at 6 months to 1 year following infection progress to AIDS much more slowly than individuals whose set point is very high at that time (Fig. 226-22).

Clinical Latency versus Microbiologic Latency With the exception of long-term nonprogressors (see "Long-Term Survivors and Long-Term Nonprogressors," below), the level of CD4+ T cells in the blood decreases progressively in HIV-infected individuals in the absence of cART. The decline in CD4+ T cells may be gradual or abrupt, the latter usually reflecting a significant spike in the level of plasma viremia. Most patients are relatively asymptomatic while this progressive decline is taking place (see below) and are often described as being in a state of *clinical latency*. However, this term is misleading; it does not mean disease latency, since progression, although slow in many cases, is generally relentless during this period. Furthermore, clinical latency should not be confused with microbiologic latency, since varying levels of virus replication inevitably occur during this period of clinical latency. Even in those rare patients who have <50 copies of HIV RNA per milliliter in the absence of therapy, there is virtually always some degree of ongoing virus replication.

ADVANCED HIV DISEASE

In untreated patients or in patients in whom therapy has not adequately controlled virus replication, after a variable period, usually measured in years, the CD4+ T cell count falls below a critical level (<200/μL) and the patient becomes highly susceptible to opportunistic disease (Fig. 226-17). For this reason, the CDC case definition of AIDS includes all HIV-infected individuals over 5 years of age with CD4+ T cell counts below this level (Table 226-2). Patients may experience constitutional signs and symptoms or may develop an opportunistic disease abruptly without any prior symptoms, although the latter scenario is unusual. The depletion of CD4+ T cells continues to be progressive and unrelenting in this phase. It is not uncommon for CD4+ T cell counts in the untreated patient to drop to as low as 10/μL or even to zero. In countries where cART and prophylaxis and treatment for opportunistic infections are readily accessible to such patients, survival is increased dramatically even in those patients with advanced HIV disease. In contrast, untreated patients who progress to this severest form of immunodeficiency usually succumb to opportunistic infections or neoplasms (see below).

LONG-TERM SURVIVORS AND LONG-TERM NONPROGRESSORS

It is important to distinguish between the terms *long-term survivor* and *long-term nonprogressor*. Long-term nonprogressors are by definition long-term survivors; however, the reverse is not always true. Predictions from one study that antedated the availability of effective cART estimated that ~13% of homosexual/bisexual men who were infected at an early age may remain free of clinical AIDS for >20 years. Many of these individuals may have progressed in their degree of immune deficiency; however, they certainly survived for a considerable period of time. With the advent of effective cART, the survival of HIV-infected individuals has dramatically increased. Early in the AIDS epidemic, prior to the availability of therapy, if a patient presented with a life-threatening opportunistic infection, the median survival was 26 weeks from the time of presentation. Currently, an HIV-infected 20-year-old individual in a high-income country who is appropriately treated with cART can expect to live at least 50 years according to mathematical model projections. In the face of cART, long-term survival is becoming commonplace. Definitions of

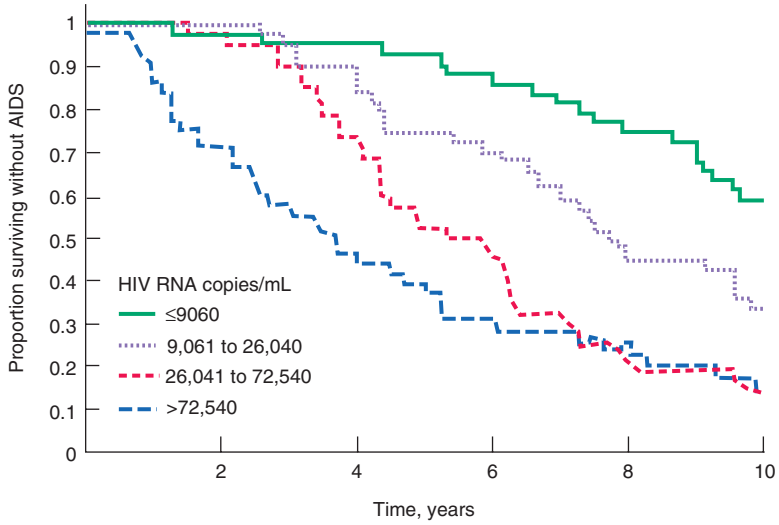

FIGURE 226-22 Relationship between levels of virus and rates of disease progression. Kaplan-Meier curves for AIDS-free survival stratified by baseline HIV-1 RNA categories (copies per milliliter). *(From JW Mellors et al: Science 272:1167, 1996.)*